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exhibits a neuropsychological disorder.

28. (New) The cell of claim 5 wherein the target gene sequence is about 70 percent homologous to SEQ ID NO: 1.

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29. (New) The cell of claim 5 wherein the target gene sequence homologously recombines with a region of SEQ ID NO: 2.

30. (New) The cell of claim 5 wherein the target gene sequence homologously recombines with a region of SEQ ID NO: 3.

31. (New) The transgenic mouse of claim 8, wherein the disruption is heterozygous.

32. (New) The transgenic mouse of claim 8, wherein the disruption is homozygous.

REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 1-15 and 17-26 were examined. Claims 1-15 and 17-26 were rejected. Claims 1-11, 13, 18-26 and 28-32 are pending after entry of the amendments set forth herein. Claims 12, 14, 15 and 17 have been canceled.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached is captioned "**Version with markings to show changes made.**"

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

Support for the amendments to claims 1-11 can be found throughout the specification, at, for example, page 3, line 14, page 6, lines 19 and 22-24, page 14, lines 14-20. Support for the amendments to claims 13, 18-26 can be found throughout the specification, at, for example, page 3, line 14, page 6, lines 19 and 22-24, page 14, lines 14-20. Support for the amendments to claims 28-32 can be found throughout the specification, at, for example, page 51, lines 13-19. As such, no new matter has been added.

Drawings.

Applicants have corrected the left margin of Figure 2B to comply with the 2.5 cm margin requirement of 37 C.F.R. § 1.84(g). As requested in the "Attachment for PTO-948," a corrected drawing is submitted as a separate paper with a transmittal letter addressed to the Official Draftsperson. A copy of the corrected drawing is enclosed herewith.

Rejection under 35 U.S.C. § 112, 1st paragraph.

Claims 5-15 and 17-26 stand rejected under 35 U.S.C. § 112, 1st paragraph for assertedly being non-enabling for "a knockout mouse comprising any disruption in any stefin homolog gene and for any cell comprising any disruption in a stefin homolog gene."

Claims 12, 14, 15 and 17 are canceled by this amendment. Claims 5-11, 13 and 18-26, as amended hereby, are now directed to a cell or transgenic mouse having a target gene sequence disrupted by homologous recombination using a sequence homologous to a region of SEQ ID NO: 1. Accordingly, the cell or transgenic mouse compositions referred to in the above-mentioned claims encompass a genome that is capable of homologous recombination or has undergone homologous recombination with a sequence homologous to SEQ ID NO: 1. As such, the amended claims are not concerned, as the Examiner asserts in rejecting claims 5-15 and 17-26, with "any disruption in any stefin homolog gene." Therefore, Applicants submit that the rejection of the above-cited claims under 35 U.S.C. § 112, first paragraph, is overcome in view of the amendments and remarks set forth herein. The Examiner is thus respectfully requested to withdraw this rejection.

Rejection under 35 U.S.C. § 112, 2nd paragraph.

Claims 12 and 14-15 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants hereby cancel claims 12, 14 and 15. As such, these rejections are rendered moot by the cancellation of the above-

mentioned claims. Thus, the Applicants request that these rejections be withdrawn.

Rejection under 35 U.S.C. § 103(a).

Claims 1-15 and 17-26 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Tsui *et al.* (*Genomics* Vol. 15, No. 3, 507-514 (1993)) and Pennachio et. al. (*Nature Genetics* Vol. 20, No. 3, 251-258 (1998)), further in view of Cappecchi *et al.* (*TIG* Vol. 5, No. 3, 70-76 (1989)), or, alternately, as being unpatentable over Sasaki *et al.* (*Genomics* Vol. 49, No. 2, 167-179 (1998)) and Pennachio et. al. (*Nature Genetics* Vol. 20, No. 3, 251-258 (1998)), in view of Cappecchi *et al.* (*TIG* Vol. 5, No. 3, 70-76 (1989))..

> "To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation . . . to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) **must teach or suggest all the claim limitations**."
> MPEP § 2143.

The Office Action asserts that, because Tsui *et al.* describes a nucleotide sequence of a murine stefin homolog gene and Pennachio *et al.* describes a knockout mouse deficient in stefin-family member Cystatin B, one of ordinary skill in the art would have been motivated to generate a knockout mouse having a disruption in the present stefin homolog gene, and one would have had a reasonable expectation of success from the combined teachings of the references. The Office Action further asserts that methods of generating knockout mice in general are described by Capecchi.

The Office Action also asserts that, because Sasaki *et al.* describes the nucleotide sequence of SEQ ID NO: 1 and Pennachio *et al.* describes a knockout mouse deficient in stefin-family member Cystatin B, one of ordinary skill in the art would have been motivated to generate a knockout mouse having a disruption in a stefin homolog gene, and one would have had a reasonable expectation of success from the combined teachings

of the references. The Office Action further asserts that the methods of generating mice are described by Capecchi.

Claims 12, 14, 15 and 17 are canceled by this amendment. Claims 1-11, 13 and 18-26, as amended, are directed to a cell or transgenic mouse having a target gene sequence disrupted by homologous recombination using a sequence homologous to a region of SEQ ID NO: 1. Neither the Tsui *et. al.* nor the Sasaki *et al.* reference is concerned with knockout mice. According to the mouse model of Pennacchio *et al.*, the reference is concerned with "early proteolytic events involved in controlling granule cell formation and preservation." (Pennacchio *et. al.* page 257, col. 1) As a result, the focus of Pennacchio *et. al.* is to generate an Unverricht-Lundborg disease phenotype ("EPM1") in mutant mice, in which a lack of cystatin B on granule cells provides insight about the pathogenesis of EPM1. The reference is not concerned with a homologous recombination event relating to SEQ ID NO: 1. As such, Pennacchio *et al.* does not contain any teaching or suggestion of homolgous recombination with SEQ ID NO: 1 to generate a stefin homolog knockout mouse. Thus, Pennacchio *et al.* is deficient in making the presently claimed invention obvious.

Cappecchi *et al.* has been cited for its generalized description of methods for the generation of knockout mice. As such, the reference is not concerned with stefin homolog knockout mice. In other words, Cappecchi *et al.* does not contain any teaching or suggestion for the generation of a stefin homolog knockout mouse, much less the use of SEQ ID NO: 1 for the generation of a stefin homolog knockout mouse. Thus, Cappecchi *et al.* fails to make up the fundamental deficiency of Pennacchio *et al.*

In view of the cited references, no prima facie case of obviousness has been established. Furthermore, one of ordinary skill in the art would not have been motivated to generate a knockout mouse via homolgous recombination with SEQ ID NO: 1. Accordingly, presently pending claims 1-11, 13 and 18-26, as amended, are not obvious under 35 U.S.C. § 103(a) over Tsui *et al.* or Sasaki *et al.*, and Pennacchio *et. al.* in view of Cappecchi *et al.*, and this rejection should be withdrawn.

Conclusion.

Applicants submit that all of the pending claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1271.

Respectfully submitted,
DELTAGEN, INC.

Date: 10/21/02

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Amended) A targeting construct capable of homologous recombination with SEQ ID NO: 1, comprising:

   (d) a first polynucleotide sequence homologous to a stefin homolog gene;

   (e) a second polynucleotide sequence homologous to the stefin homolog gene; and

   (f) a selectable marker.

2. The targeting construct of claim 1, wherein the targeting construct further comprises a screening marker.

3. (Amended) A method of producing a targeting construct capable of homologous recombination with SEQ ID NO: 1, the method comprising:

   (e) providing a first polynucleotide sequence homologous to a stefin homolog gene;

   (f) providing a second polynucleotide sequence homologous to the stefin homolog gene;

   (g) providing a selectable marker; and

   (h) inserting the first sequence, second sequence, and selectable marker into a vector, to produce the targeting construct.

4. (Amended) A method of producing a targeting construct capable of homologous recombination with SEQ ID NO: 1, the method comprising:

   (c) providing a polynucleotide comprising a first sequence homologous to a first region of a stefin homolog gene and a second sequence homologous to a second region of a stefin homolog gene; and

   (d) inserting a positive selection marker between the first and second sequences to form the targeting construct.

5. (Amended) A cell comprising a genome comprising a target gene sequence disrupted by homologous recombination of the target gene sequence with [disruption in a stefin homolog gene] a sequence homologous to a region of SEQ ID NO: 1.

6. The cell of claim 5, wherein the cell is a murine cell.

7. The cell of claim 6, wherein the murine cell is an embryonic stem cell.

8. (Amended) A [non-human] transgenic [animal] mouse comprising a genome comprising a target gene sequence disrupted by homologous recombination of the target gene sequence with [disruption in a stefin homolog gene] a sequence homologous to a region of SEQ ID NO: 1.

9. A cell derived from the non-human transgenic animal of claim 8.

10. (Amended) A method of producing a transgenic mouse comprising a genome comprising a target gene sequence disrupted by homologous recombination of the target gene sequence with [disruption in a stefin homolog gene] a sequence homologous to a region of SEQ ID NO: 1, the method comprising:

(e) introducing the targeting construct of claim 1 into a cell;

(f) introducing the cell into a blastocyst;

(g) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and

(h) breeding the chimeric mouse to produce the transgenic mouse.

11. (Amended) A method of identifying an agent that modulates the expression of a stefin homolog, the method comprising:

(d) providing the [a non-human] transgenic [animal] mouse of claim 8 [comprising a disruption in a stefin homolog gene];

(e) administering an agent to the non-human transgenic animal; and

(f) determining whether the expression of stefin homolog in the mouse [non-human transgenic animal] is modulated.

Claim 12 has been canceled.

13. (Amended) A method of identifying an agent that modulates the expression of stefin homolog, the method comprising:

(d) providing the [a] cell of claim 5 [comprising a disruption in a stefin homolog gene];

(e) contacting the cell with an agent; and

(f) determining whether expression of the stefin homolog is modulated.

Claim 14 has been canceled.

Claim 15 has been canceled.

Claim 17 has been canceled.

18. (Amended) The transgenic mouse of claim 8 [17], wherein the transgenic mouse exhibits increased activity, relative to a wild-type mouse.

19. The transgenic mouse of claim 18, wherein the transgenic mouse is hyperactive.

20. The transgenic mouse of claim 18, wherein the increased activity is characterized by increased velocity of movement in an open-field test, relative to a wild-type mouse.

21. (Amended) The transgenic mouse of claim 8 [17], wherein the transgenic mouse exhibits decreased propensity for despair or depression, relative to a wild-type mouse.

22. The transgenic mouse of claim 21, wherein the decreased propensity for despair or depression is characterized by decreased immobile time in a tail suspension test, relative to a wild-type mouse.

23. (Amended) The transgenic mouse of claim 8 [17], wherein the transgenic mouse exhibits a stimulus-processing deficit relative to a wild-type mouse.

24. The transgenic mouse of claim 18, wherein the stimulus-processing deficit is characterized by decreased pre-pulse inhibition.

25. (Amended) The transgenic mouse of claim 8 [17], wherein the transgenic mouse exhibits schizophrenic behavior.

26. (Amended) The transgenic mouse of claim 8 [17], wherein the transgenic mouse exhibits a neuropsychological disorder.

28. (New) The cell of claim 5 wherein the target gene sequence is at least about 70 percent homologous to SEQ ID NO: 1.

29. (New) The cell of claim 5 wherein the target gene sequence homologously recombines with a region of SEQ ID NO: 2.

30. (New) The cell of claim 5 wherein the target gene sequence homologously recombines with a region of SEQ ID NO: 3.

31. (New) The transgenic mouse of claim 8, wherein the disruption is heterozygous.

32. (New) The transgenic mouse of claim 8, wherein the disruption is homozygous.